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ORIGINAL REPORT

Pralatrexate in Patients With Relapsed or Refractory Peripheral T-Cell Lymphoma: Results From the Pivotal PROPEL Study

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ABSTRACT

Purpose
Peripheral T-cell lymphoma (PTCL) is a poor prognosis subtype of non-Hodgkin's lymphoma with no accepted standard of care. This study evaluated the efficacy and tolerability of pralatrexate, a novel antifolate with promising activity.

Patients and Methods
Patients with independently confirmed PTCL who progressed following ≥ 1 line of prior therapy received pralatrexate intravenously at 30 mg/m^2/wk for 6 weeks in 7-week cycles. Primary assessment of response was made by independent central review using the International Workshop Criteria. The primary end point was overall response rate. Secondary end points included duration of response, progression-free survival (PFS), and overall survival (OS).

Results
Of 115 patients enrolled, 111 were treated with pralatrexate. The median number of prior systemic therapies was three (range, 1 to 12). The response rate in 109 evaluable patients was 29% (32 of 109), including 12 complete responses (11%) and 20 partial responses (18%), with a median DoR of 10.1 months. Median PFS and OS were 3.5 and 14.5 months, respectively. The most common grade 3/4 adverse events were thrombocytopenia (32%), mucositis (22%), neutropenia (22%), and anemia (18%).

Conclusion
To our knowledge, PROPEL (Pralatrexate in Patients with Relapsed or Refractory Peripheral T-Cell Lymphoma) is the largest prospective study conducted in patients with relapsed or refractory PTCL. Pralatrexate induced durable responses in relapsed or refractory PTCL irrespective of age, histologic subtypes, amount of prior therapy, prior methotrexate, and prior autologous stem-cell transplant. These data formed the basis for the US Food and Drug Administration approval of pralatrexate, the first drug approved for this disease.

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INTRODUCTION

Peripheral T-cell lymphoma (PTCL) represents a heterogeneous group of mature T- and natural killer (NK) -cell neoplasms, accounting for 10% to 15% of newly diagnosed cases of non-Hodgkin's lymphoma (NHL) in North America.[1-4] Based on the WHO classification, mature T- and NK-cell neoplasms are subclassified into 22 distinct disease entities, the most common of which include PTCL not otherwise specified (NOS), angioimmunoblastic (AILT), and anaplastic large-cell lymphoma.[5]

In contrast to B-cell NHL, PTCLs are more resistant to conventional chemotherapy and are generally associated with an inferior outcome except for anaplastic lymphoma kinase (ALK) + anaplastic large-cell lymphoma. Numerous studies have reported a poorer survival for patients with PTCL, with a median overall survival (OS) of shorter than 2 years and a 5-year survival less than 30%.[4,6-8] The 2-year failure-free survival for patients with high- or intermediate-high risk disease is estimated at 10%.[7-9] Even with autologous stem-cell transplantation (ASCT), 5-year progression-free survival (PFS) and OS rates have been reported to be as low as 24% and 33%, respectively.[10-11] These outcomes are notably inferior to those for patients with even the most aggressive B-cell lymphomas. While the precise biologic reasons for the differences between B- and T-cell lymphomas are not clear, many explanations

have been advanced, including: differences in intrinsic chemosensitivity, the fact that patients with PTCL typically have a higher International Prognostic Index at presentation, and the absence of drugs with unique activity in PTCL. Importantly, all regimens presently employed for PTCL are derived from B-cell lymphoma experiences.[12-14] These data underscore the urgent need for new treatment options for patients with PTCL, especially those with recurrent or refractory disease, who typically have limited responses to salvage therapy and extremely poor OS.[9]

Pralatrexate is an antifolate that was designed to be efficiently internalized by the reduced folate carrier (RFC). In addition, because it is a superior substrate for folylpolyglutamyl synthetase, pralatrexate is more effectively polyglutamylated and retained, minimizing extrusion via natural efflux pumps. The RFC is an oncofetal protein that is expressed on both embryonic and malignant tissues that regulates the internalization of natural folates required for purine and pyrimidine biosynthesis. It is hypothesized that the high affinity of pralatrexate for RFC leads to selective tumor cell accumulation. Preclinical data have clearly established the superiority of pralatrexate over other antimetabolites.[15-17]

Early clinical experience with pralatrexate in patients with relapsed or refractory B- or T-cell NHL established the tolerability and efficacy of a weekly schedule with vitamin supplementation.[18] This early trial revealed an overall response rate (ORR) of 31%, although among patients with T-cell lymphoma, the ORR was 54%. Furthermore, all of the eight complete responses (CRs) seen were in patients with PTCL, while four of six partial responses (PR) were positron emission tomography (PET) negative.

These data led to the design of the PROPEL (Pralatrexate in Patients with Relapsed or Refractory Peripheral T-Cell Lymphoma) trial, a phase II, single-arm, open-label, international multicenter study.

PATIENTS AND METHODS

Study Design and Treatment

PROPEL enrolled patients from 25 centers between August 2006 and April 2008. Vitamin supplementation consisting of B_{12} 1 mg intramuscular every 8 to 10 weeks and daily oral folic acid 1.0 to 1.25 mg was required to ameliorate mucositis as demonstrated in the earlier experience. Elevated methylmalonic acid ($>$ 200 nmol/L) and/or homocysteine ($>$ 10 μmol/L) at screening required initiation of vitamins $\geq$ 10 days before the first dose of pralatrexate.

Pralatrexate was administered as an intravenous push over 3 to 5 minutes at 30 mg/m^2/wk for 6 weeks followed by 1 week of rest (7-week cycle). Treatment was continued until progressive disease (PD), unacceptable toxicity, or patient/physician discretion. A dose omission or reduction to 20 mg/m^2/wk was permitted on meeting prespecified safety criteria.

The primary end point of the study was ORR (CR + CR unconfirmed [CRu] + PR). Secondary end points included duration of response (DoR), PFS, and OS. The protocol-specified requirement for scan frequency was every 14 weeks during treatment and then every 12 weeks thereafter until PD or subsequent therapy.

Review boards or ethics committees at all participating institutions approved the study, which was conducted according to the provisions of the Declaration of Helsinki and its current amendments, and the International Conference on Harmonization Guidelines for Good Clinical Practice. All patients provided written informed consent. All study investigators are listed in the Appendix (online only).

Patients

Patients $\geq$ 18 years of age with PTCL according to the Revised European American Lymphoma WHO disease classification (Appendix Table A1, online only) were eligible for study.[19] Patients were required to have documented disease progression after $\geq$ 1 prior treatment and recovered from the toxic effects of prior therapy. At least 4 weeks must have lapsed between receipt of prior chemotherapy or radiation therapy and the initiation of pralatrexate. There was no upper limit on the amount of prior therapy. Additional criteria included an Eastern Cooperative Oncology Group performance status $\leq$ 2 and adequate hematologic, hepatic, and renal function (absolute neutrophil count $\geq$ 1,000/μL, platelet count $\geq$ 100,000/μL, total bilirubin $\leq$ 1.5 mg/dL, AST and ALT $\leq$ 2.5$\times$ upper limit of normal, and creatinine $\leq$ 1.5 mg/dL). Patients were not excluded if they had pleural effusions or ascites at entry.

Patients were ineligible if they had other prespecified T/NK-cell neoplasms (Appendix Table A1). Additional exclusion criteria included: prior allogeneic stem-cell transplant (SCT); relapse less than 75 days after ASCT; major surgery within 2 weeks of study entry; investigational drugs, biologics, or devices as the only prior therapy, and any conventional chemotherapy or radiation therapy $\leq$ 4 weeks before study treatment.

Assessments

PTCL was confirmed based on histopathologic evaluation by independent central pathology review and adjudicated by an independent third-party expert hematopathologist, if necessary. ORR was assessed with a rigorous process of central review of imaging and clinical data according to the International Workshop Criteria (IWC) developed by the National Cancer Institute–sponsored International Working Group.[20] Response assessments were performed within 7 days before the projected first dose of the second cycle and then within 7 days before the projected first dose of every even-numbered subsequent cycle. In addition, unscheduled response assessments were submitted for central review. PET scans also were collected and evaluated in an exploratory analysis.

Additional assessments included physical examination with skin photography and bone marrow aspirate/biopsy and post-treatment tumor biopsies, if indicated, as well as laboratory blood tests (CBCs and basic metabolic panels).

Safety was assessed at every study visit by evaluating changes in hematologic and biochemical parameters and by monitoring the incidence, severity, and relationship of adverse events (AEs) to pralatrexate. AEs were graded using the National Cancer Institute Common Toxicity Criteria for Adverse Events scale, version 3.0 and were coded using the Medical Dictionary for Regulatory Activities version 11.0. Platelet transfusions, erythropoietin, and hematopoietic growth factors were allowed at the discretion of the investigator.

After discontinuing treatment, patients attended a safety follow-up visit 35 $\pm$ 5 days after the last dose of pralatrexate, and routine follow-up visits every 3 months ($\pm$ 2 weeks) thereafter until PD or subsequent treatment for PTCL was initiated. Patients were observed for survival and subsequent treatment for PTCL every 6 months for a total of 2 years.

Statistical Analysis

A two-stage, Simon design was employed.[21] Enrollment into stage 2 was based on a determination that $\geq$ four of 35 evaluable patients enrolled in stage 1 were responders. At least 23 of 100 patients must have responded to enable a 95% CI to exclude 15%. With 100 patients, this two-stage design had 84% power to reject the null hypothesis of a 15% response rate, assuming a priori a true response rate of 27%.

An independent data monitoring committee reviewed clinical data after the first 10 patients completed cycle 1 (safety review); after 35 patients completed cycle 1 (safety and response review); and after $\geq$ 65 patients completed cycle 1 (safety review).

DoR was measured from first day of documented response to PD or death. Patients receiving subsequent therapy (including transplant) or withdrew consent before PD were censored as of the last prior response assessment. Patients who withdrew from treatment before PD or subsequent therapy without withdrawing consent were observed for disease status. PFS and OS were measured from treatment day 1 until event or censoring. Patients receiving subsequent therapy before documented PD were censored for PFS. Efficacy end points were analyzed using the patient population evaluable for efficacy (ie, $\geq$ 1 dose of pralatrexate and a confirmed diagnosis of an eligible

histopathologic PTCL subtype). The study data analysis cutoff date was August 2009.

RESULTS

Patient Characteristics

Twenty-five centers in the United States, Europe, and Canada enrolled 115 patients; 111 received ≥ 1 dose of pralatrexate and were evaluable for safety, and 109 were evaluable for efficacy. Two patients were deemed ineligible because they did not have a confirmed diagnosis of PTCL. Table 1 presents baseline characteristics of all 111 patients. In general, these demographics reflect the characteristics of patients with PTCL in the western hemisphere. The median age was 58 (range, 21 to 85) and 72% of patients were white. The majority of patients (53%) had PTCL-NOS, though most subtypes were represented. Patients were heavily pretreated before enrollment, with a

Table 1. Baseline Characteristics of Patients

Parameter	Patients (N = 111)	
	No.	%
Sex		
Male	76	68
Female	35	32
Ethnicity		
White	80	72
African American	14	13
Asian	6	5
Hispanic	9	8
Other	1	< 1
Unknown	1	< 1
Mean age, years	57.7	
Range	21-85	
≥ 65	40	36
Median No. of prior therapies for PTCL	3	
Range	1-13	
Median No. of prior systemic therapies for PTCL	3	
Range	1-12	
Type of prior therapy for PTCL		
Local therapy		
Radiation therapy	25	23
Photopheresis	10	9
Topical nitrogen mustard	4	4
Systemic therapy		
CHOP	78	70
Platinum-containing multi-agent chemotherapy	45	41
Non-platinum-containing multi-agent chemotherapy	43	39
Single-agent chemotherapy	36	32
Autologous stem cell transplant	18	16
Bexarotene	15	14
Other	13	12
Corticosteroids alone*	8	7
HyperCVAD	8	7
Denileukin diftitox	7	6
Systemic investigational agents	7	6
Histopathology per central review		
PTCL unspecified	59	53
Anaplastic large cell lymphoma, primary systemic type*	17	15
Angioimmunoblastic T-cell lymphoma	13	12
Transformed mycosis fungoides	12	11
Blastic NK lymphoma (with skin, lymph node, or visceral involvement)	4	4
Other	2†	2
T/NK-cell lymphoma nasal	2	2
Extranodal peripheral T/NK-cell lymphoma unspecified	1	< 1
Adult T-cell leukemia/lymphoma (HTLV-1$^+$)	1	< 1

NOTE. Patients treated with corticosteroids alone received other systemic therapies.
Abbreviations: PTCL, peripheral T-cell lymphoma; CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone; HyperCVAD, hyperfractionated cyclophosphamide with vincristine, doxorubicin, and corticosteroids; NK, natural killer; HTLV, human T-lymphotropic virus; ALK, anaplastic lymphoma kinase.
*Eleven patients were ALK negative, four were ALK positive, two did not have ALK status determined.
†Ineligible for study due to diagnosis of mycosis fungoides not transformed and nondiagnostic pathologic lymphoid infiltrate.

Table 2. Best Response to Treatment and Time-to-Event Data

Response and Time to Event (Total N = 109)	Central Review				Local Investigator	
	IWC		IWC + PET			
	No.	%	No.	%	No.	%
Best response						
CR + CRu + PR	32	29	28	26	43	39
CR	11	10	15	14	17	16
CRu	1	1	0	0	3	3
PR	20	18	13	12	23	21
SD	21	19	18	17	21	19
PD	40	37	31	28	40	37
UE	2	2	18	17	0	0
Missing, off treatment in cycle 1	14	13	14	13	5	5
Time-to-event	32		28		43	
Median time to response, days						
First response	46		48		50	
Range	37-349		37-248		38-358	
Best response	141		136		51	
Range	37-726		37-542		38-542	
Median duration of response, months	10.1		12.7		8.1	
Median duration of response, days	306		386		246	

Abbreviations: IWC, International Workshop Criteria; PET, positron emission tomography; CR, complete response; CRu, complete response unconfirmed; PR, partial response; SD, stable disease; PD, progressive disease; UE, unevaluable.

median of three prior systemic therapies (range, 1 to 12). Importantly, in the population eligible for efficacy, 24% (n = 26) did not demonstrate any evidence of response to any prior therapy, while 63% (n = 69) did not have evidence of response to their most recent prior therapy. Sixteen percent (n = 18) relapsed after ASCT. Median time from diagnosis to study entry was 15.6 months.

Efficacy

In the evaluable patient population (n = 109), the ORR was 29% (95% CI, 21% to 39%) as assessed by independent central review (Table 2).[20] Twelve patients (11%) achieved CR/CRu, 20 (18%) achieved PR, and 21 (19%) experienced stable disease. Of the 69 patients who did not have any evidence of response to their most recent prior therapy, 17 (25%) responded to pralatrexate. Of the 26 patients who did not have evidence of response to any prior conventional therapy, five (19%) responded to pralatrexate. Response rates for other key subsets are summarized in Table 3.

When IWC was supplemented with PET scans, the response rate was 26% (n = 28; 14% CR and 12% PR). Ninety-three patients (85%) had a positive baseline PET scan, 13 (12%) had a negative baseline PET result, and three (3%) did not have PET scans. ORR as judged by the local investigators was 39% (18% CR/CRu and 21% PR).

The majority of responding patients attained response quickly; 63% of all responses occurred within the first cycle of pralatrexate, but responses were observed as late as cycle 7. While the median duration of treatment was 70 days (95% CI, 39 to 86), the median duration of treatment among responders was 186 days (95% CI, 132 to 429).

Figure 1A presents the waterfall plot for patients with bidimensional disease at baseline and at least 1 post-treatment assessment (n = 88). Seventy-six percent of these patients (n = 67) exhibited a decrease in tumor volume, with 18% of patients experiencing an increase in their disease volume after pralatrexate.

The median DoR was 10.1 months (306 days; 95% CI, 3.4 months to not estimable) with a range of 1 to 673 days (Fig 1B, Table 2). Among the 32 responders 16 (50%) progressed or died, five (16%) were still in response, and 11 (34%) were censored as follows: four transplant (two autologous and two allogeneic), subsequent therapy (n = 3), or study termination (n = 4). Interestingly, only two patients

Table 3. Response Analyses by Key Subsets

Parameter	No.	%	IWC Response Rate		
			No.	%	95% CI
Region					
North America	85	78	27	32	22 to 43
Europe	24	22	5	21	7 to 42
Age, years					
< 65	70	64	19	27	17 to 39
≥ 65	39	36	13	33	19 to 50
Prior systemic therapy					
1 regimen	23	21	8	35	16 to 57
2 regimens	29	27	7	24	10 to 44
> 2 regimens	57	52	17	30	18 to 43
Prior transplant					
Yes	18	17	6	33	13 to 59
No	91	83	26	29	20 to 39
Prior methotrexate					
Yes	21	19	5	24	8 to 47
No	88	81	27	31	21 to 41
Histology					
PTCL NOS	59	54	19	32	21 to 46
Angioimmunoblastic	13	12	1	8	0 to 36
Anaplastic LC	17	16	6	35	14 to 62
Transformed MF	12	11	3	25	5 to 57
Other	8	7	3	38	9 to 76

Abbreviations: IWC, International Workshop Criteria; PTCL, peripheral T-cell lymphoma; NOS, not otherwise specified; LC, large cell; MF, mycosis fungoides.

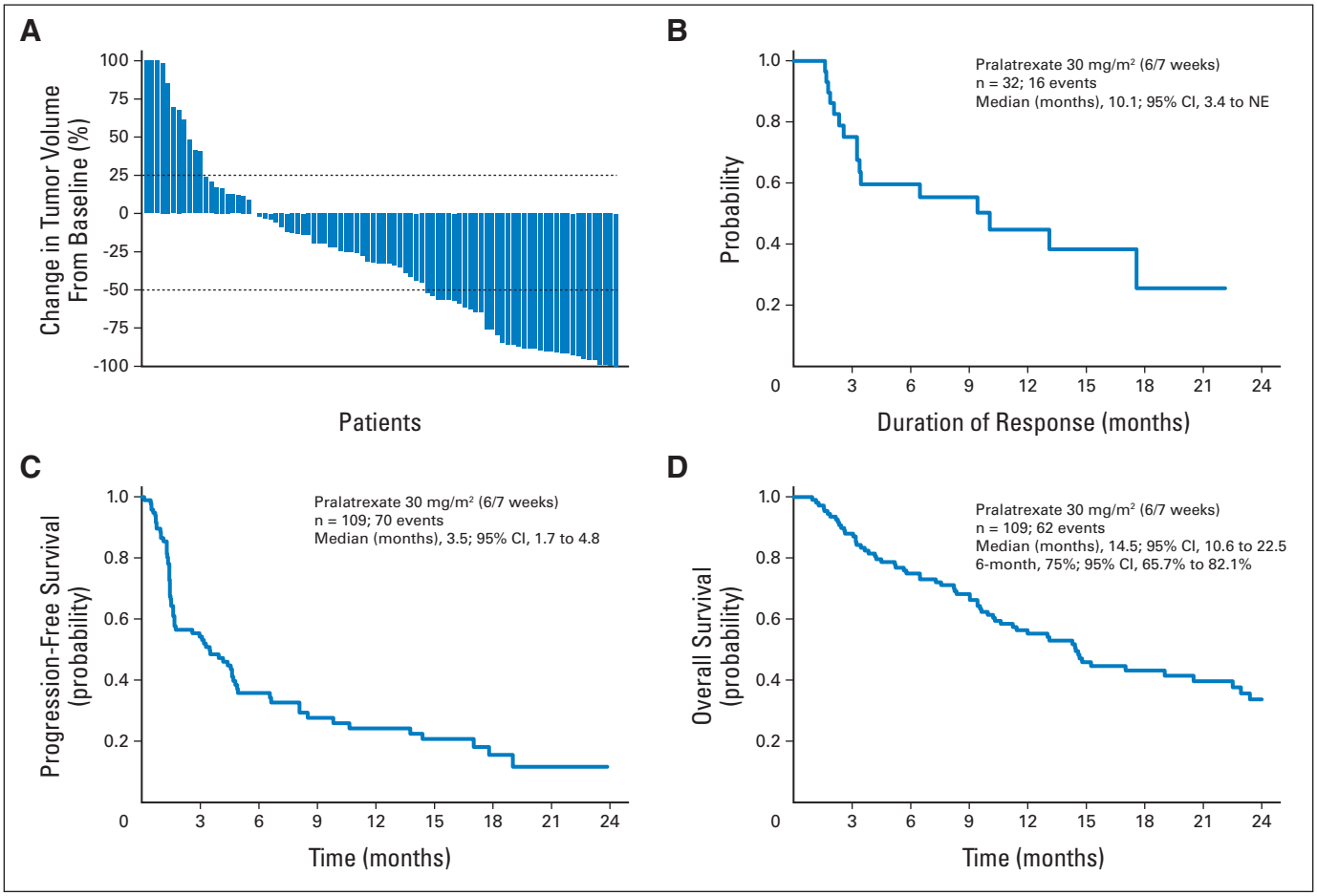

Fig 1. (A) Maximum change from baseline in tumor volume (sum of the products of the greatest diameter). (B) Kaplan-Meier estimate of duration of response per central review. (C) Kaplan-Meier estimate of progression-free survival per central review. (D) Kaplan-Meier estimate of overall survival per central review.

who attained a CR developed PD. Nine patients had responses exceeding 300 days in duration, four of whom remained on treatment at the time of data cutoff. At the time of last follow-up, all four of the patients still in response (three CR, one PR) at the time of SCT remained alive and had received no further therapy.

The median PFS was 3.5 months (95% CI, 1.7 to 4.8), with a range of 1 day to 23.9 months (Fig 1C). The median OS was 14.5 months (95% CI, 10.6 to 22.5), with a range of 1.0 to 24.1 months (Fig 1D). Forty-seven patients (43%) were censored for OS because they were still alive at the data cutoff date. Median follow-up time for all patients still alive at the time of the analysis was 18 months.

Safety

The majority of patients in this study tolerated pralatrexate. The overall relative dose intensity (delivered *v* planned doses administered) was 80%. Seventy-six patients (68%) remained at the target dose of 30 mg/m^2 for the duration of treatment, and 76 (68%) had one or more dose omissions due to AEs. Mucositis was the most common reason for dose modification. Specifically, 25 patients (23%) were dose reduced for mucositis. Other reasons for dose reduction were liver function test abnormal, thrombocytopenia, and fatigue (two patients each, 2%), and herpes zoster, leucopenia, neutropenia, and rash pruritic (one patient each, $< 1\%$).

The most common AEs were mucositis, nausea, thrombocytopenia, and fatigue. The most common grade 3 or 4 AEs were thrombocytopenia, mucositis, neutropenia, and anemia. Other frequently reported AEs were mainly mild to moderate in severity (Table 4). Forty-five percent (n = 50) experienced serious AEs while on study or $\leq$ 30 days after their last dose of pralatrexate. The most common serious AEs included pyrexia (7%), mucositis (5%), febrile neutropenia (5%), sepsis (5%), dehydration (4%), and dyspnea (4%). The majority of AEs were reversible or manageable by dose modification. No cumulative myelosuppression was observed with continued pralatrexate treatment. Thrombocytopenia, anemia, and neutropenia rarely were symptomatic and required supportive care in a minority of patients; 15% of patients received a platelet transfusion and 10% received filgrastim.

Twenty-three percent (n = 26) withdrew from treatment due to AEs, most frequently for mucositis (6%) or thrombocytopenia (5%). Eight patients (7%) in the study died within 30 days of their last dose of pralatrexate. Seven of eight patients died due to PD and one patient experienced a cardiopulmonary arrest approximately 3 weeks after the last dose of pralatrexate while hospitalized for mucositis and febrile neutropenia. This death was deemed possibly related to pralatrexate.

Table 4. Adverse Events (safety population) in ≥ 10% of Patients

Event	Total		Grade 3		Grade 4	
	No.	%	No.	%	No.	%
Any event	111	100	47	42	35	32
General events and administration site conditions						
Mucositis*	79	71	20	18	4	4
Fatigue	40	36	6	5	2	2
Pyrexia	38	34	1	1	1	1
Edema*	34	31	1	1	0	0
Hematologic events						
Thrombocytopenia*†	45	41	15	14	21	19
Anemia*	38	34	18	16	2	2
Neutropenia*	28	25	15	14	9	8
Leukopenia*	12	11	4	4	4	4
GI events						
Nausea	46	41	4	4	0	0
Constipation	38	34	0	0	0	0
Vomiting	28	25	2	2	0	0
Diarrhea	25	23	2	2	0	0
Dyspepsia*	11	10	0	0	0	0
Respiratory, thoracic, and mediastinal events						
Cough	32	29	1	1	0	0
Epistaxis	29	26	0	0	0	0
Dyspnea	21	19	8	7	0	0
Skin and subcutaneous tissue events						
Rash	17	15	0	0	0	0
Pruritus*	16	14	2	2	0	0
Night sweats	12	11	0	0	0	0
Infections						
Upper respiratory tract infection	12	11	1	1	0	0
Sinusitis	11	10	1	1	0	0
Other conditions						
Hypokalemia*	18	16	4	4	1	1
Anorexia*	18	16	3	3	0	0
Pharyngolaryngeal pain	15	14	1	1	0	0
Liver function test abnormal*	14	13	6	5	0	0
Back pain	14	13	3	3	0	0
Abdominal pain	13	12	4	4	0	0
Headache	13	12	0	0	0	0
Pain in extremity	13	12	0	0	0	0
Asthenia	12	11	2	2	0	0
Tachycardia	11	10	0	0	0	0

NOTE. Patients could have > 1 adverse event. Included in this Table are all patients who received ≥ 1 dose of the study drug.
*Included a grouping of similar preferred terms.
†Platelet count < 10,000 μL was seen in five patients.

DISCUSSION

The prognosis for patients with newly diagnosed aggressive peripheral T-cell lymphoma is poor for most subtypes. PTCLs have the lowest 5-year survival rates among NHL subtypes, including mantle-cell lymphoma. There is little to no consensus regarding the optimal treatment of patients in the first-line, let alone relapsed or refractory setting. While there have been numerous, small, single-agent studies in which patients showed some response to therapy, these have not been validated in large rigorous centrally reviewed (ie, pathology or response trials). Therefore, patients with relapsed or refractory disease have limited therapeutic options.

To our knowledge, PROPEL is the largest prospective multicenter trial with an independent central review of both histology and response to date in patients with relapsed or refractory PTCL. The study evaluated a very heavily treated patient population, which included 24% of patients with no evidence of response to any prior therapy, and 63% of patients who had no evidence of response to the treatment immediately before study registration. Despite the heavily pretreated nature of the population, pralatrexate produced an ORR of 29%, with 11% CRs. When assessed by the treating investigator, the ORR was 39%. Interestingly, the CR rate as assessed by PET was 14%. The recent integration of PET scanning into the response criteria for select subtypes of NHL, including Hodgkin's lymphoma and diffuse large B-cell lymphoma, suggests that attaining a PET-negative response is associated with superior treatment outcomes. Of note, there is consistency of response across key baseline parameters. While PROPEL was not statistically designed to define the ORR in specific

subsets of patients, the consistency in response rate as a function of age, prior therapy, prior ASCT, prior methotrexate, and PTCL subtype, suggests pralatrexate has broad activity across the spectrum of features that often characterize this heterogeneous disease. The somewhat lower rate of response seen in AILT may reflect the unique biology of AILT, or simply the small number of patients with this subtype entered on study. Ten of 12 patients who attained a CR by IWC continue in remission suggesting a lack of cross-resistance to conventional chemotherapy. Four patients that received ASCT post-pralatrexate remain in remission suggesting that pralatrexate could be a potential bridge to definitive SCT.

Patients who responded to pralatrexate also achieved significant duration of benefit. The median DoR was 10.1 months, with more than one fourth of responses lasting longer than 300 days. This was despite the conservative assessment of DoR, which censored the four responders who received SCT although they remained in response. Survival conclusions are difficult in the absence of a randomized trial. The OS was 14.5 months in this study, whereas survival expectations in this population are generally low.

AEs associated with pralatrexate were manageable and consistent with other antifolates. The most common grade 3/4 AEs were thrombocytopenia, mucositis, neutropenia, and anemia. While 71% of patients experienced some degree of mucositis, it was manageable with dose modifications for the majority of patients. To continue therapy, patients should have a mucositis grade no worse than 1 (soreness and erythema without functional concerns). The mean duration of grade $\geq$ 2 mucositis in the treated population was 14 days. The majority of patients (68%) were able to receive pralatrexate at 30 mg/m^2 without dose reduction. AEs were generally reduced or reversed on dose modification.

Based on the results of the pivotal PROPEL trial, the US Food and Drug Administration approved pralatrexate for the treatment of patients with relapsed or refractory PTCL, making pralatrexate the first drug approved for this indication. Future areas of development have now focused on identifying synergistic combinations of other agents with pralatrexate, including gemcitabine, bortezomib, or histone deacetylase inhibitors. For example, both preclinical and clinical experiences have demonstrated marked synergy by combining pralatrexate with gemcitabine or bortezomib.[15,17] Additional areas of clinical development are focused on integrating pralatrexate into first-line PTCL treatment programs, and exploring its clinical merit in B-cell and cutaneous T-cell lymphomas.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

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